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The X-ray Crystal Structure of the Molecular Complex 9-Ethyladenine–Parabanic Acid–Oxaluric Acid Monohydrate

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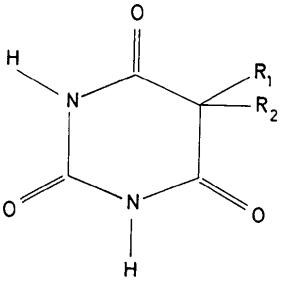
Crystals of the complex 9-ethyladenine–parabanic acid–oxaluric acid monohydrate, $C_{13}H_{17}N_9O_8$, have the space group $P\bar{1}$ with $a=6{\cdot}802$ (1), $b=13{\cdot}131$ (2), $c=11{\cdot}135$ (2) Å, $\alpha=98{\cdot}03$ (1), $\beta=112{\cdot}53$ (1) and $\gamma=98{\cdot}04$ (1)° and with two complexes per unit cell. Intensity data were measured with an automated diffractometer using graphite monochromated Cu $K\alpha$ radiation. The structure was solved by direct methods and refined by full-matrix least-squares procedures to a final $R=0{\cdot}040$ based on 2808 unique reflections. The structure consists of roughly planar layers of molecules that are extensively hydrogen bonded to one another. The parabanic acid carbonyl groups exhibit little, if any, tendency to act as hydrogen-bond acceptors. Adjacent layers of molecules stack so that there are several interatomic contacts less than the minimal van der Waals distance. These close approaches appear to be due to Coulomb interactions involving ionic charges and strong dipoles. The role of the water molecule seems to be largely that of filling a cavity in the crystal structure.

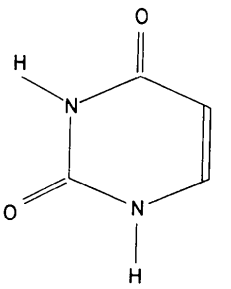
The chemical grouping most widespread in life processes is the –NH–CO– moiety. In proteins it is most notably found as the peptide bond and hence it is the major determinant of the primary and secondary structure of proteins. In the nucleic acid bases guanine and uracil the –NH–CO– groupings participate in the formation of hydrogen-bonded cyclic dimers so as to form Watson–Crick base pairs. Hence the physicochemical properties of the –NH–CO– moiety are of utmost importance in the processes of transmission and expression of genetic information.

Crystallographic information (Voet & Rich, 1970) together with physicochemical studies of nucleic acids and their components (Shoup, Miles & Becker, 1966; Kyogoku, Lord & Rich, 1966) have demonstrated that the hydrogen-bonding properties of the –NH–CO– moiety are dependent on the nature of the molecule in which it is incorporated. These studies have shown that of the four nucleic acid bases only the Watson–Crick pairs, adenine–uracil and guanine–cytosine, can form stable hydrogen-bonded base pairs.

A large class of drugs that depress nerve activity incorporate an –NH–CO– moiety. The most widely used compounds of this type are the barbiturates although chemically related sedative-hypnotic and/or anticonvulsant drugs such as the hydantoins, the acetylureas and the succinamides also contain an –NH–CO– moiety (Sharpless, 1965; Toman, 1965). Barbiturates (I) have a hydrogen-bonding affinity for adenine derivatives that is an order of magnitude greater than that of the chemically similar uracil (II) derivatives (Kyogoku, Lord & Rich, 1968; Kyogoku & Yu, 1970). This phenomenon provides the basis for the hypothesis that barbiturates interfere with the transmission of nerve impulses by their participation in hydrogen-bonded base pairs with the adenine-bearing coenzymes contained in nerve cells (Kyogoku, Lord & Rich, 1968; Kim & Rich, 1968).



(I)



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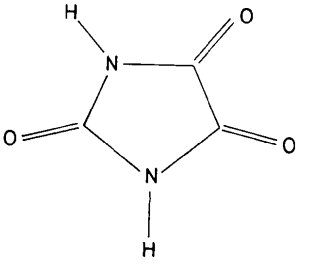
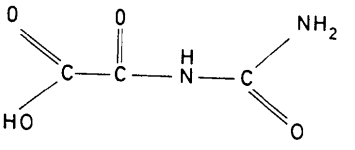


(III)



(IV)

The X-ray crystal structures of several adenine–uracil complexes as well as those of a number of adenine–barbiturate complexes have been reported (Voet & Rich, 1970; Voet, 1975). These studies indicate that whereas adenine–uracil complexes have rather ordinary and largely predictable structural parameters, those of adenine–barbiturate complexes are often rather peculiar in that they may contain exceedingly long N–H···O hydrogen bonds or anomalous hydrogen-bonding patterns. Comparisons of the X-ray structures of a number of hydrogen-bonded complexes containing barbiturates in association with various different types of molecules suggest that the hydrogen bonds involving a barbiturate amido group as the donor are rather strong whereas those involving the barbiturate carbonyl group as the acceptor are particularly weak (Gartland & Craven, 1974; Hsu & Craven, 1974).

The phenomenon of selective hydrogen bonding between nucleic acid bases and their analogues has been attributed to the electronic properties of the complexing molecules (Kyogoku, Lord & Rich, 1967). However, the quantum-chemical properties of small molecules are not, at present, sufficiently well understood so as to enable the reliable prediction of their hydrogen-bonding affinities. It is therefore desirable to acquire extensive experimental data related to the structural properties of various hydrogen-bonded base pairs. It is likely that this would enable the accurate prediction of the mutual hydrogen-bonding affinities of any two bases from consideration of their molecular formulae. Such a body of information could also be a useful guide in the development of a reliable theory of electronic specificity in hydrogen bonding. We have therefore undertaken a program to determine the structures of a number of adenine–uracil-like base pairs in which either the adenine or the uracil moiety has been chemically modified in some manner.

Parabanic acid (III) is chemically related to the barbiturates and to uracil. Although it is not in use as a drug, administration of parabanic acid produces a soporific effect (Makarina-Kibak, Korablev & Vredenskii, 1972), as might be expected from this chemical resemblance. We therefore attempted to cocrystallize parabanic acid with 9-ethyladenine. It will be seen below that the resulting crystals, which at first were thought to consist of the complex 9-ethyladenine–(parabanic acid)$_2$–2H$_2$O turned out to be 9-ethyladenine–parabanic acid–oxaluric acid–H$_2$O (A.P.X.H$_2$O). Oxaluric acid (IV) is a derivative of parabanic acid in which the parabanic acid N(1)–C(5) bond has been hydrolyzed. Therefore the two complexes have identical elemental composition.

Experimental

Crystals of A.P.X.H$_2$O, which took the form of colorless rectangular prisms elongated along their *a* axis, were grown by the slow evaporation of aqueous solutions of 9-ethyladenine (Cyclo Chemical) and what was taken to be reasonably pure parabanic acid (Eastman Kodak Co.) in 1:1, 1:2 and 1:3 molar ratios. The X-ray powder patterns of ground crystals from these three preparations were identical. The ultraviolet absorption spectrum of an aqueous solution of a washed crystal suggested that the crystals contained parabanic acid and 9-ethyladenine in a roughly 2:1 molar ratio.

A crystal of the complex with dimensions 0·2 × 0·1 × 0·1 mm, was cut from a larger crystal. The absence of any symmetry other than Friedel symmetry in preliminary Weissenberg and precession photographs of the crystal indicated that it had triclinic lattice symmetry. All subsequent X-ray measurements were made with a Picker FACS-I diffractometer equipped with a pyrolytic graphite monochromator and employing Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å). The parameters of the unit cell, as determined from the least-squares analysis of the angular positions of 12 reflections with $2\theta > 54°$, are presented in Table 1. This unit cell is convenient because, as will be seen below, the planes of the molecules are roughly parallel to its (100) plane.

Table 1. *Crystal data for* 9-*ethyladenine–parabanic acid–oxaluric acid*–H$_2$O

Molecular formula	$C_{13}H_{17}N_9O_8$
$a = 6{\cdot}802$ (1) Å	F.W. 427·33
$b = 13{\cdot}131$ (2)	Space group $P\bar{1}$
$c = 11{\cdot}135$ (2)	$Z = 2$
$\alpha = 98{\cdot}03$ (1)°	$d_{obs} = 1{\cdot}599$ g cm^{-3}
$\beta = 112{\cdot}53$ (1)	$d_{calc} = 1{\cdot}596$ g cm^{-3}
$\gamma = 98{\cdot}04$ (1)	μ(Cu $K\alpha$) = 11·7 cm^{-1}
$V = 889{\cdot}04$ Å^3	$F(000) = 444$

The buoyant density of the crystals (Table 1), as determined by flotation in a mixture of CCl_4 and 1,4-dibromobutane, is in good agreement with the calculated density for the unit cell containing two complexes of composition 9-ethyladenine–(parabanic acid)$_2$–2H$_2$O (or equally well, 9-ethyladenine–parabanic acid–oxaluric acid–H$_2$O).

The X-ray diffraction data were measured to the limit $2\theta = 125°$ using the θ–2θ scan mode, a scan rate of 1° min^{-1}, a scan width of 1·2° and a take-off angle of 2·5°. Stationary background counts of 20s each were taken at both limits of each scan.

Structure determination and refinement

The measured intensities, *I*, were corrected for Lorentz and polarization effects. No absorption corrections were made owing to the small size of the crystal and its low linear absorption coefficient for Cu $K\alpha$ radiation. Standard deviations, $\sigma(I)$, were calculated (Stout & Jensen, 1968) assuming an instrumental instability factor of 0·02. Of the 2808 measured unique reflections, 107 had $I < 2{\cdot}33\sigma(I)$. The remainder are observed at the 98% confidence level.

The normalized structure factors, *E*, were calculated

using the method of polynomial regression to determine $\langle I \rangle$ as a function of $\sin \lambda/\theta$ (Voet, 1972). The distribution of the E's (Karle & Hauptman, 1956) together with the zero moment plot (Howells, Phillips & Rogers, 1950) clearly suggested that the space group of the crystal contained a center of symmetry. Hence the space group was assumed to be $P\bar{1}$. This assumption was subsequently confirmed by the successful refinement of the structure.

The crystal structure was solved by direct methods using the program *MULTAN* (Main, Woolfson & Germain, 1971). The correct phase set was elucidated by first determining the signs of the 126 reflections with $|E| > 2{\cdot}0$ and then extending these phases to develop the signs of the remaining 191 reflections with $|E| > 1{\cdot}6$. The E map based on the correct phase set, which contained the expected 20 strong peaks, clearly revealed the 9-ethyladenine and a single parabanic acid molecule. The expected second parabanic acid ring appeared to have opened up. At this point a perusal of the chemical literature revealed that parabanic acid is hydrolyzed to oxaluric acid at room temperature (Andrews & Sell, 1955). The thermal behavior of the sample of parabanic acid used in this study (melting with decomposition at 223–228 °C *vs.* melting at 245–247 °C reported by Andrews & Sell (1955) for pure parabanic acid) together with its ultraviolet spectrum clearly indicated that the sample was not pure parabanic acid. Accordingly, the unassigned peaks in the E map were taken to be oxaluric acid and a water molecule.

The structure was refined by the full-matrix least-squares method. The atomic scattering factors for non-hydrogen atoms were taken from Cromer & Waber (1965) and those for hydrogen atoms were taken from Stewart, Davidson & Simpson (1965). Isotropic followed by anisotropic refinement of the structure reduced R from its initial value of 0·381 to 0·074. A difference map calculated at this point revealed all the hydrogen atoms in their expected positions except for those of the water molecule. These latter two atoms could not be conclusively located. Subsequent refinement in which the thermal parameters of the non-hydrogen atoms were treated anisotropically and those of the hydrogen atoms were treated isotropically caused the discrepancy indices to converge to their final values of $R = 0{\cdot}040$ and $R_w = 0{\cdot}053$ based on all 2808 reflections.* The final parameter shifts were all less than the

* A table of observed and calculated structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30993 (13 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Positional and thermal parameters for the complex 9-ethyladenine–parabanic acid–oxaluric acid*–H_2O

The positional parameters are expressed as fractions of unit-cell edges. The anisotropic temperature factors have the functional form $T = \exp[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23}) \times 10^{-4}]$. Isotropic temperature factors have the functional form $T = \exp(-B \sin^2\theta/\lambda^2)$. Standard deviations, as determined from the variance–covariance matrix of the final cycle of least-squares refinement are given in parentheses and refer to the least significant digits of their corresponding parameters. The prefixes A, P, X and W of the atom designators refer to the 9-ethyladeninium, the parabanic acid, the oxalurate and the water molecules, respectively.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
AN(1)	0·2829 (2)	0·0341 (1)	0·7635 (1)	211 (4)	29 (1)	54 (1)	18 (1)	48 (2)	5 (1)
AC(2)	0·2523 (3)	−0·0604 (1)	0·7965 (2)	208 (5)	36 (1)	57 (2)	21 (2)	48 (2)	13 (1)
AN(3)	0·2135 (2)	−0·1513 (1)	0·7186 (1)	218 (4)	33 (1)	60 (1)	21 (1)	50 (2)	11 (1)
AC(4)	0·2058 (3)	−0·1417 (1)	0·5977 (2)	168 (4)	29 (1)	54 (2)	19 (2)	37 (2)	7 (1)
AC(5)	0·2401 (2)	−0·0491 (1)	0·5553 (2)	157 (4)	29 (1)	52 (2)	16 (2)	34 (2)	7 (1)
AC(6)	0·2826 (2)	0·0463 (1)	0·6442 (2)	143 (4)	32 (1)	52 (2)	17 (2)	34 (2)	8 (1)
AN(7)	0·2246 (2)	−0·0706 (1)	0·4269 (1)	227 (4)	35 (1)	55 (1)	18 (2)	52 (2)	6 (1)
AC(8)	0·1819 (3)	−0·1739 (1)	0·3946 (2)	223 (5)	35 (1)	57 (2)	18 (2)	49 (2)	2 (1)
AN(9)	0·1687 (2)	−0·2211 (1)	0·4934 (1)	222 (4)	28 (1)	61 (1)	20 (1)	49 (2)	3 (1)
AN(6)	0·3179 (2)	0·1412 (1)	0·6211 (2)	262 (5)	26 (1)	58 (1)	14 (2)	59 (2)	6 (1)
AC(1′)	0·1175 (3)	−0·3347 (1)	0·4883 (2)	302 (6)	25 (1)	92 (2)	29 (2)	71 (3)	7 (1)
AC(2′)	−0·1111 (4)	−0·3704 (2)	0·4715 (3)	361 (8)	30 (1)	151 (3)	12 (2)	127 (4)	5 (2)
PN(1)	0·2009 (3)	−0·3012 (1)	0·8909 (2)	300 (15)	33 (1)	71 (2)	20 (2)	58 (2)	17 (1)
PC(2)	0·2003 (3)	−0·4077 (1)	0·8665 (2)	348 (7)	36 (1)	65 (2)	17 (2)	63 (3)	8 (1)
PN(3)	0·2337 (3)	−0·4414 (1)	0·9833 (2)	323 (5)	29 (1)	78 (2)	21 (2)	75 (2)	13 (1)
PC(4)	0·2575 (3)	−0·3616 (1)	1·0824 (2)	270 (6)	37 (1)	70 (2)	19 (2)	68 (3)	11 (1)
PC(5)	0·2310 (3)	−0·2648 (1)	1·0178 (2)	212 (5)	33 (1)	75 (2)	12 (2)	47 (2)	8 (1)
PO(2)	0·1766 (4)	−0·4598 (1)	0·7630 (2)	845 (10)	55 (1)	80 (2)	58 (3)	130 (3)	4 (1)
PO(4)	0·2925 (3)	−0·3625 (1)	1·1967 (1)	499 (6)	63 (1)	79 (2)	49 (2)	112 (3)	24 (1)
PO(5)	0·2366 (2)	−0·1775 (1)	1·0705 (1)	337 (5)	33 (1)	112 (2)	28 (1)	76 (2)	3 (1)
XN(1)	0·2418 (3)	0·0534 (1)	1·2319 (2)	288 (5)	38 (1)	66 (2)	19 (2)	66 (2)	16 (1)
XC(2)	0·2854 (3)	0·1568 (1)	1·2747 (2)	176 (5)	40 (1)	60 (2)	26 (2)	50 (2)	14 (1)
XO(2)	0·3257 (2)	0·2009 (1)	1·3885 (1)	325 (4)	48 (1)	60 (1)	31 (2)	75 (2)	13 (1)
XN(3)	0·2845 (2)	0·2194 (1)	1·1817 (1)	246 (5)	29 (1)	60 (1)	27 (2)	59 (2)	9 (1)
XC(4)	0·2711 (3)	0·1868 (1)	1·0577 (2)	226 (5)	34 (1)	60 (2)	26 (2)	52 (2)	9 (1)
XO(4)	0·2609 (3)	0·0962 (1)	1·0097 (1)	520 (6)	35 (1)	78 (1)	54 (2)	120 (2)	14 (1)
XC(5)	0·2697 (3)	0·2732 (1)	0·9760 (2)	210 (5)	33 (1)	62 (2)	15 (2)	52 (2)	9 (1)
XO(5)	0·2978 (2)	0·2459 (1)	0·8735 (1)	328 (4)	48 (1)	68 (1)	28 (2)	86 (2)	17 (1)
XO(6)	0·2410 (3)	0·3584 (1)	1·0223 (1)	464 (6)	35 (1)	101 (2)	49 (2)	128 (2)	23 (1)
WO	0·3812 (4)	0·4468 (1)	1·3284 (2)	614 (8)	81 (1)	164 (3)	53 (3)	153 (4)	37 (2)

Table 2 (*cont.*)

	x	*y*	*z*	*B*
AH(1)	0·297 (3)	0·089 (2)	0·820 (2)	3·1 (4)
AH(2)	0·262 (3)	−0·057 (1)	0·887 (2)	2·6 (4)
AH(3)	0·159 (3)	−0·218 (1)	0·305 (2)	2·1 (3)
AH(4)	0·347 (3)	0·195 (2)	0·683 (2)	3·2 (4)
AH(5)	0·321 (3)	0·152 (2)	0·543 (2)	3·4 (4)
AH(6)	0·225 (4)	−0·344 (2)	0·578 (2)	4·3 (5)
AH(7)	0·152 (3)	−0·372 (2)	0·417 (2)	3·5 (4)
AH(8)	−0·136 (4)	−0·326 (2)	0·546 (3)	6·1 (6)
AH(9)	−0·219 (5)	−0·361 (2)	0·386 (3)	7·1 (7)
AH(10)	−0·149 (4)	−0·445 (2)	0·471 (2)	5·2 (6)
PH(1)	0·188 (4)	−0·264 (2)	0·827 (3)	4·7 (5)
PH(2)	0·241 (4)	−0·512 (2)	0·989 (2)	4·6 (5)
XH(1)	0·240 (4)	0·012 (2)	1·292 (2)	4·3 (5)
XH(2)	0·212 (4)	0·025 (2)	1·144 (2)	4·0 (5)
XH(3)	0·298 (3)	0·281 (2)	1·206 (2)	2·7 (4)

estimated standard deviations of their respective parameters.

The molecular structures

The molecular configuration of the complex A.P.X.H_2O is illustrated in Fig. 1 together with the atomic numbering system used in this report. Table 2 contains the final fractional coordinates and thermal parameters for all of the atoms in the asymmetric unit of the unit cell together with their standard deviations as estimated from the variance-covariance matrix of the final least-squares refinement. Fig. 2 presents the covalent bond distances and angles of the structure.

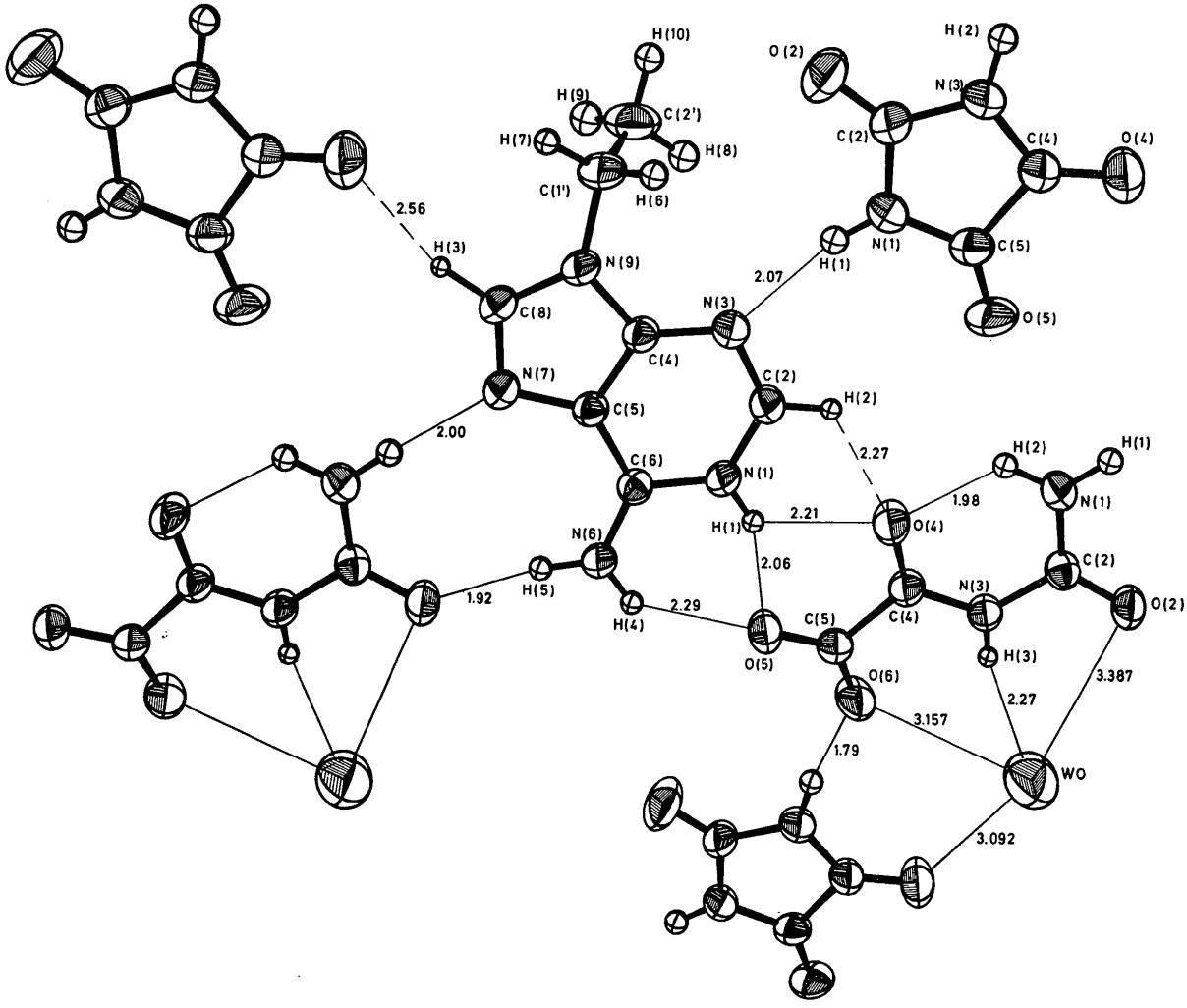


Fig. 1. A perspective drawing of the crystalline complex 9-ethyladenine–parabanic acid–oxaluric acid–H_2O viewed roughly along the *a* axis. This illustrates the hydrogen-bonding pattern of the complex. Non-hydrogen atoms are represented by thermal ellipsoids at the 50% probability level. Hydrogen atoms are drawn as spheres at the 25% probability level. Hydrogen bonds and C–H···O hydrogen-bond-like interactions are shown as thin lines and dashed lines, respectively, accompanied by their distances in Å.

Table 3. *The bonding parameters for fifteen accurately determined structures containing* N(1)*-protonated adenine residues, their averages and standard deviations and the averages and standard deviations of the corresponding parameters of neutral adenine residues*

(*a*) Bond distances (Å)

Adeninium compound	Ref.[f]	1–2	2–3	3–4	4–5	5–6	6–1	5–7	7–8	8–9	9–4	6–N6	9–1′
Adenosine hydrochloride	1	1·361	1·308	1·353	1·384	1·397	1·353	1·375	1·307	1·382	1·362	1·325	1·460
5′-AMP	2	1·368	1·312	1·341	1·403	1·448	1·362	1·364	1·328	1·398	1·377	1·312	1·492
3′-AMP.$2H_2O$	3	1·349	1·306	1·353	1·381	1·401	1·363	1·384	1·312	1·368	1·355	1·319	1·477
$Na_2ATP.3H_2O$[a]	4	1·37	1·31	1·34	1·40	1·45	1·36	1·36	1·33	1·40	1·38	1·31	1·51
5′-Methylene-cyclic-AMP.H_2O	5	1·360	1·314	1·364	1·372	1·408	1·356	1·385	1·305	1·383	1·375	1·320	1·455
$Cu_3Cl_8(AdeH)_2.4H_2O$	6	1·323	1·334	1·383	1·371	1·394	1·377	1·375	1·320	1·330	1·361	1·319	–
$ZnCl_3(AdeH)$	7	1·364	1·283	1·360	1·379	1·415	1·363	1·385	1·313	1·343	1·350	1·302	–
$[Co(H_2O)_4(Ade)_2]\,(AdeH)_2(SO_4)_2.6H_2O$	8	1·361	1·307	1·360	1·375	1·396	1·381	1·378	1·318	1·364	1·352	1·313	–
$[Cu(AdeH)_2Br_2]Br_2$	9	1·357	1·304	1·376	1·364	1·411	1·346	1·377	1·329	1·315	1·385	1·331	–
2′,5′-ApU	10	1·350	1·306	1·351	1·382	1·401	1·370	1·389	1·313	1·396	1·358	1·320	1·446
UpA, molecule 1[b]	11	1·356	1·331	1·353	1·394	1·433	1·374	1·348	1·319	1·377	1·387	1·291	1·505
UpA, molecule 2[b]	11	1·341	1·282	1·380	1·352	1·417	1·399	1·389	1·317	1·385	1·375	1·301	1·475
Puromycin.$2HCl.5H_2O$	12	1·342	1·295	1·358	1·360	1·436	1·370	1·401	1·300	1·363	1·376	1·317	1·468
3′-Methylene-3′-AMP	13	1·376	1·305	1·366	1·354	1·411	1·371	1·375	1·330	1·375	1·376	1·332	1·470
A.P.X.H_2O		1·354	1·301	1·352	1·385	1·403	1·359	1·378	1·314	1·361	1·365	1·314	1·471
Average[d]		1·344	1·307	1·359	1·377	1·415	1·367	1·378	1·317	1·370	1·369	1·315	1·475
σ[e]		0·013	0·014	0·013	0·015	0·019	0·013	0·013	0·009	0·025	0·012	0·011	0·020
Average of 7 neutral adenine residues[d]	14	1·332	1·315	1·349	1·365	1·404	1·346	1·388	1·297	1·365	1·370	1·341	1·479
σ of 7 neutral adenine residues[e]	14	0·022	0·008	0·011	0·014	0·012	0·027	0·018	0·021	0·016	0·018	0·023	0·021

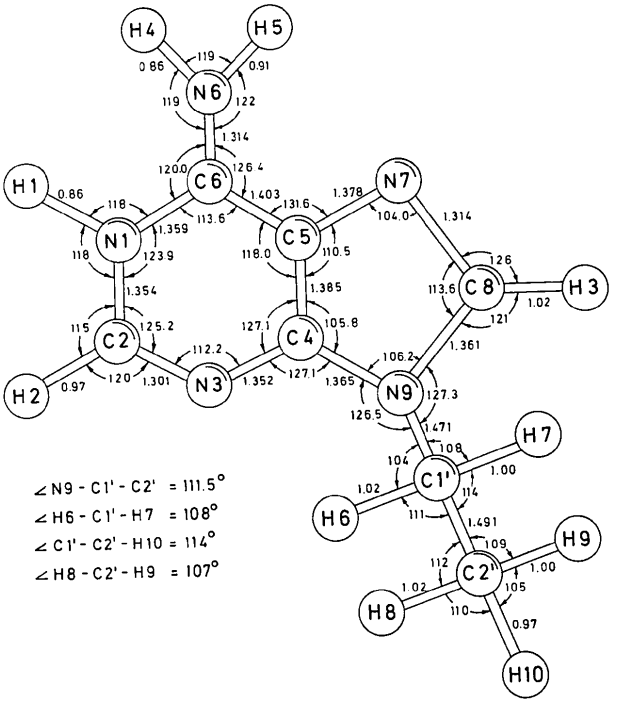
(*b*) Bond angles (°)

	6–1–2	1–2–3	2–3–4	3–4–5	4–5–6	5–6–1	3–4–9	6–5–7	5–7–8	7–8–9	8–9–4	9–4–5	4–5–7	1–6–N6	5–6–N6	4–9–1′	8–9–1′
Adenosine hydrochloride	124·2	125·0	111·6	127·4	118·2	113·5	127·0	130·5	103·8	113·6	105·8	105·6	111·3	120·4	126·1	126·7	127·6
5′AMP	122·8	125·7	112·3	128·5	115·6	114·7	127·4	131·9	104·7	111·8	107·1	104·1	112·3	121·5	123·7	123·8	128·6
3′-AMP.$2H_2O$	123·3	125·9	111·6	127·2	118·2	113·7	127·3	130·6	103·3	113·4	106·6	105·4	111·2	120·2	126·1	125·2	128·0
$Na_2ATP.3H_2O$[a]	123	126	113	129	116	115	128	132	105	112	107	104	112	122	124	126	126
5′-Methylene-cyclic-AMP.H_2O	123·5	125·2	111·6	127·5	117·8	114·2	127·0	130·5	103·6	113·6	105·7	105·5[c]	111·7	121·6	124·2	129·8	124·5
$Cu_3Cl_8(AdeH)_2.4H_2O$	124·3	124·9	113·3	123·3	121·6	112·5	127·2	131·5	105·3	114·2	104·1	109·5	106·8	122·0	125·4	–	–
$ZnCl_3(AdeH)$	124·6	124·8	112·7	127·1	118·1	112·6	126·8	132·3	104·2	113·0	107·2	106·1	109·5	120·6	126·8	–	–
$[Co(H_2O)_4(Ade)_2]\,(AdeH)_2(SO_4)_2.6H_2O$	123·4	124·6	112·4	127·7	117·9	114·0	126·3	130·6	102·8	113·8	106·0	106·0	111·5	120·7	125·3	–	–
$[Cu(AdeH)_2Br_2]Br_2$	124·4	124·8	112·7	125·4	119·7	113·0	125·1	133·2	105·0	114·9	103·6	109·4	107·1	121·6	125·4	–	–
2′,5′-ApU	123·6	125·2	112·4	126·8	118·4	113·5	126·9	131·2	104·8	111·9	106·6	106·2	110·5	120·8	125·7	124·4	129·0
UpA, molecule 1[b]	124·0	126·2	109·4	130·8	115·7	113·7	126·0	130·5	103·5	113·3	106·4	103·2	113·6	121·4	124·9	126·1	126·9
UpA, molecule 2[b]	121·4	127·8	111·5	127·1	118·4	113·6	126·4	130·0	103·6	112·9	105·4	106·5	111·6	122·3	124·1	126·0	128·5
Puromycin.$2HCl.5H_2O$	123·8	127·6	109·5	129·4	117·5	111·8	124·0[c]	131·5	102·7	115·2	104·7	106·6	110·8	120·2	127·9	125·6	129·7
3′-Methylene-3′-AMP	122·5	125·7	111·1	128·7	117·9	114·0	124·3	131·4	104·8	111·9	105·7	107·0	110·7	118·7	127·3	127·6	126·8
A.P.X.H_2O	123·9	125·2	112·2	127·1	118·0	113·6	127·1	131·6	104·0	113·6	106·2	105·8	110·5	120·0	126·4	126·5	127·3
Average[d]	123·5	125·6	111·8	127·5	117·9	113·6	126·5	131·3	104·1	113·3	105·9	106·1	110·7	120·9	125·6	126·2	127·5
σ[e]	0·8	1·0	1·1	1·7	1·5	0·8	1·2	0·9	0·8	1·1	1·1	1·7	1·8	1·0	1·2	1·6	1·5
Average of 7 neutral adenine residues[d]	118·6	129·1	111·0	127·0	117·3	117·3	127·4	132·4	103·8	113·8	105·7	106·1	110·3	119·1	123·5	126·1	128·4
σ of 7 neutral adenine residues[e]	1·4	1·5	1·0	0·4	0·9	1·6	0·9	1·1	1·2	1·4	0·7	0·7	0·8	0·7	0·7	1·6	1·1

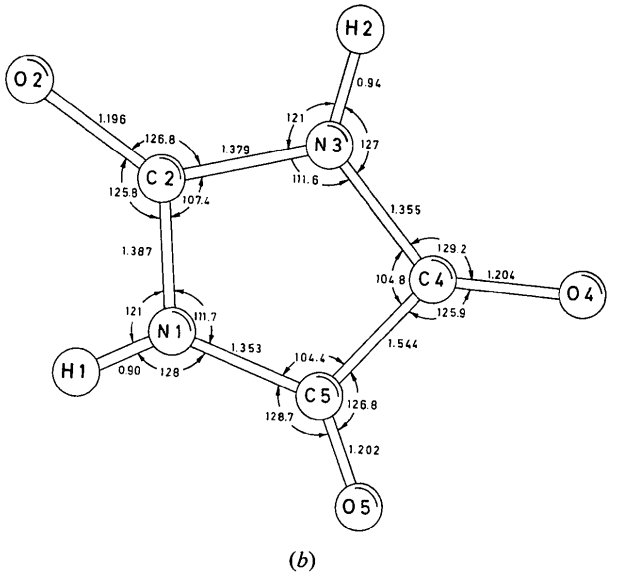
[a]The two independent adeninium residues in the asymmetric unit of $Na_2ATP.3H_2O$ were constrained to be equivalent in their least-squares refinement. The values for molecule *B* only were used for those bond parameters involving atom C(1′) because the corresponding parameters for molecule *A* appeared to be badly distorted. [b]There are two independent molecules of UpA in the asymmetric unit. [c]This parameter has been recalculated due to an erroneous value in the original reference. [d]The averages were taken with unit weights due to the reality of the variation of a given bond parameter among related structures. The averaging process was not constrained to ensure ring closure. [e]Standard deviations, σ, are calculated in the usual manner: $\sigma = \sqrt{[\sum_{i=1}^{n}(x_i-\bar{x})^2/(n-1)]}$. [f]References: (1) Shikata, Ueki & Mitsui (1973); (2) Kraut & Jensen (1963); (3) Sundaralingam (1966); (4) Kennard *et al.* (1971); (5) Sundaralingam & Abola (1972); (6) de Meester & Skapski (1972); (7) Taylor (1973); (8) de Meester & Skapski (1973b); (9) de Meester & Skapski (1973*a*); (10) Shefter, Barlow, Sparks & Trueblood (1969); (11) Sussman, Seeman, Kim & Berman (1972); (12) Sundaralingam & Arora (1972); (13) Hecht & Sundaralingam (1972); (14) Voet & Rich (1970).

(i) 9-*Ethyladeninium ion*

Structural studies of numerous adeninium compounds indicate that the adenine residue is first protonated at its N(1) position. The present study concurs

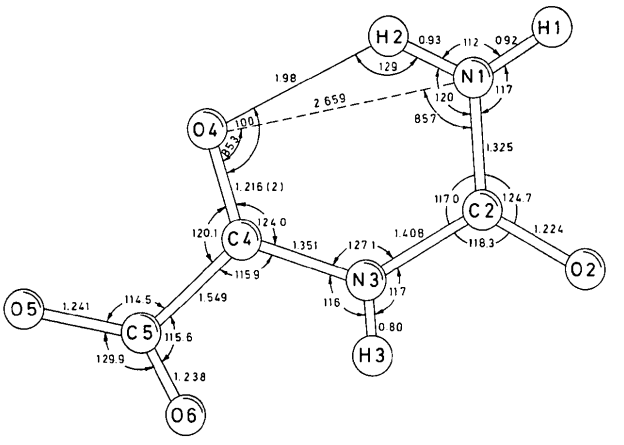


(*a*)



(*b*)

Fig. 2. The covalent bond distances (Å) and angles (°) of (*a*) the 9-ethyladeninium ion, (*b*) the parabanic acid molecule in the complex A.P.X.H_2O. The estimated standard deviations of these quantities are 0·002 Å and 0·2°, respectively, for bonds not involving hydrogen atoms and 0·02 Å and 1°, respectively, for bonds involving hydrogen atoms.



(*c*)

Fig. 2 (*cont.*). (*c*) The covalent bond distances (Å) and angles (°) of the oxalurate ion in A.P.X.H_2O. For e.s.d.'s see legend to Fig. 2 (*a*) and (*b*).

Table 4. *Deviations of atoms from the least-squares plane through the indicated atoms*

Equations of the least-squares planes

Adeninium plane:
$6{\cdot}3741x - 2{\cdot}4324y - 0{\cdot}4148z = 1{\cdot}4180$ Å.

Parabanic acid plane:
$6{\cdot}4617x + 0{\cdot}4269y - 1{\cdot}7650z = -0{\cdot}4087$ Å.

Urea plane:
$6{\cdot}5745x - 2{\cdot}1452y - 1{\cdot}5019z = 0{\cdot}3749$ Å.

Peptide plane:
$6{\cdot}3125x - 0{\cdot}4217y - 0{\cdot}5643z = 1{\cdot}0363$ Å.

Acetate plane:
$5{\cdot}6348x + 1{\cdot}2395y + 1{\cdot}2138z = 3{\cdot}0403$ Å.

Adeninium atom	Deviation (Å)	Parabanic acid atom	Deviation (Å)
N(1)	−0·014	N(1)	0·006
C(2)	0·007	C(2)	0·000
N(3)	0·013	N(3)	−0·005
C(4)	−0·009	C(4)	0·008
C(5)	0·002	C(5)	−0·008
C(6)	0·003	O(2)	0·007*
N(7)	0·008	O(4)	0·032*
C(8)	0·001	O(5)	−0·028*
N(9)	−0·010	R.m.s.	
N(6)	0·007*	deviation	0·006
C(1′)	−0·057*		
R.m.s. deviation	0·009		

Oxalurate atom	Urea plane deviation (Å)	Peptide plane deviation (Å)	Acetate plane deviation (Å)
N(1)	0·000	−0·228*	−0·119*
C(2)	0·000	−0·020*	0·307*
O(2)	0·000	0·151*	0·727*
N(3)	0·000	0·000	0·266*
O(4)	0·367*	0·000	−0·228*
C(4)	0·168*	−0·001	0·000
C(5)	0·096*	0·000	0·000
O(5)	0·493*	0·247*	0·000
O(6)	−0·345*	−0·243*	0·000
R.m.s. deviation	0·000	0·000	0·000

* Atoms not included in calculating the least-squares plane.

with this finding. The bond distances and bond angles of 15 accurately determined adeninium derivatives are presented in Table 3. It can be seen that the bonding parameters of the adeninium residue in the present structure are in excellent agreement with those of other such residues. The adeninium ring, as can be seen from Table 4, is nearly planar, although some of the ring atoms deviate significantly from their mean plane.

(ii) *Parabanic acid*

It can be seen from Fig. 2 that the molecular twofold symmetry of the parabanic acid molecule is preserved in the crystal structure to within experimental error with the possible exception of a slight distortion about atom C(2). The bond distances and bond angles of the parabanic acid molecule are in reasonable agreement with the corresponding parameters of parabanic acid molecules reported in other structural studies (Davies & Blum, 1955; Colman & Medlin, 1970*a*, *b*). Table 4 indicates that the imidazole ring is planar to almost within experimental error. However atoms O(4) and O(5) are displaced significantly to opposite sides of the imidazole ring.

(iii) *Oxalurate ion*

The oxalurate ion, which is a condensation product of the oxalate ion with urea, can be considered to be composed of three overlapping sections: a urea moiety [atoms N(1), C(2), O(2) and N(3)], a peptide unit [atoms N(3), C(4), O(4) and C(5)] and an acetate moiety [atoms C(4), C(5), O(5) and O(6)]. This can be seen in Table 4 which reveals that these individual groupings are planar to within experimental error although the oxalurate ion as a whole is rather non-planar. The urea and the acetate planes form dihedral angles with the peptide plane of $-12{\cdot}6°$ and $9{\cdot}7°$, respectively. The latter angle, due to the nearly perfect planarities of the peptide and acetate groupings, is identical with the torsional angle O(4)–C(4)–C(5)–O(5). The N(1)–C(2)–N(3)–C(4) torsion angle is $9{\cdot}1°$. There is good agreement between the analogous bonding parameters in the urea moiety of the oxalurate ion and those of urea (Caron & Donohue, 1969), urea–5,5-diethylbarbituric acid (Gartland & Craven, 1974), $(urea)_2$–oxalic acid (Harkema, Bats, Weyenberg & Feil, 1973), urea–parabanic acid (Colman & Medlin, 1970*a*), perdeuterated biuret hydrate (Craven, 1973) and triuret (Ringertz, 1966); in the peptide unit of oxaluric acid and the average of several peptides compiled by Marsh & Donohue (1967); and in the acetate moiety of oxaluric acid and those of the various oxalate structures compiled by Küppers (1973).

The conformation of the oxalurate ion is stabilized by a strong but distorted N(1)–H(2)···O(4) intramolecular hydrogen bond that is illustrated in Fig. 1. Similar interactions have been observed in the structures of biuret (Craven, 1973) and triuret (Ringertz, 1966). In these latter molecules the planes of the urea moieties are distorted from coplanarity with one another in a manner similar to that of the urea and peptide moieties in the oxalurate ion. This distortion appears to be due to van der Waals repulsions between the closely approaching donor nitrogen atom and the acceptor oxygen atom in the decidey non-linear intramolecular hydrogen bond.

(iv) *The intermolecular interactions*

The structure is composed of alternating centrosymmetrically related layers of planar molecules. The different types of planar molecules or molecular fragments within the individual layers are significantly non-parallel. The dihedral angle between the adenine least-squares plane and that of parabanic acid is $13{\cdot}5°$; those

Table 5. *Non-covalent bonding interactions*

(*a*) Hydrogen bonds

Hydrogen bond *D*–H···*A*	Distance (Å) *D*···*A*	Distance (Å) H···*A*	Angle (°) *D*–H···*A*
(1) Normal hydrogen bonds			
AN(6)—AH(5)····XO(2*a*)	2·826	1·92	170
XN(1*a*)–XH(1*a*)···AN(7)	2·917	2·00	176
AN(6)—AH(4)····XO(5)	3·013	2·29	142
PN(1)—PH(1)····AN(3)	2·948	2·07	166
PN(3*b*)–PH(3*b*)···XO(6)	2·727	1·79	170
XN(1)—XH(2)····XO(4)*	2·659	1·98	129
XN(3)—XH(3)····WO	3·046	2·27	164
(2) Bifurcated hydrogen bonds			
AN(1)–AH(1)···XO(4)	2·815	2·21	127
AN(1)–AH(1)···XO(5)	2·850	2·06	153
(3) C–H···O hydrogen bond-like interactions			
AC(2)–AH(2)···XO(4)	2·891	2·27	121
AC(8)–AH(3)···PO(4*a*)	3·437	2·56	143
(4) Close water–donor contacts			
WO···XO(2)	3·387		
WO···XO(6)	3·157		
WO···PO(4*b*)	3·092		

(*b*) Stacking interactions among non-hydrogen atoms

(1) Contacts less than their corresponding minimal van der Waals distance

PC(5)····XO(5*c*)	2·919 Å
PC(4)····XO(5*c*)	3·011
AC(2′)···PO(2*d*)	3·032
AC(4)···XC(2*c*)	3·246

(2) Other contacts less than 3·3 Å

AN(1)···PO(5*c*)	3·212 Å
AC(2)···XN(1*e*)	3·269
AN(9)···XO(2*c*)	3·132
PN(1)···XC(5*c*)	3·269
PO(5)···XO(5*c*)	3·266
PC(5)···XO(6*e*)	3·108
PC(4)···XO(6*e*)	3·143
PO(5)···XC(4*e*)	3·167

Lower case letters accompanying atom numbers refer to atoms related to those in Table 2 by the following symmetry operations

(*a*)	$x, y, -1+z$	(*d*)	$-x, -1-y, 1-z$
(*b*)	$x, 1+y, z$	(*e*)	$-x, -y, 2-z$
(*c*)	$1-x, -y, 2-z$		

* Intramolecular hydrogen bond.

between the adenine plane and the urea, peptide and acetate planes of the oxalurate ion are 5·8°, 9·0° and −19·5°, respectively. Hence the individual layers of molecules are rather rumpled.

The individual layers are joined together by a complex network of hydrogen bonds and C–H···O hydrogen-bond-like interactions so that all of the hydrogen atoms in the structure, with the exception of those on the adenine ethyl group, are involved in such interactions. The hydrogen bonding parameters are presented in Fig. 1 and in Table 5.

The adenine residue associates with the oxaluric acid amine group through a cyclic dimer in which both hydrogen bonds are of normal length and of reasonable linearity. Adeninium atom H(1) forms a bifurcated hydrogen bond with atoms O(4) and O(5) of an oxaluric acid molecule that is translationally related to the forgoing one. The XO(4)–AH(1)–XO(5) angle is 78°. Oxaluric acid atom O(5) also takes part in a distorted and somewhat elongated hydrogen bond with the adenine amine group. These interactions are supplemented by a C–H···O hydrogen-bond-like interaction between the adenine C(2)–H(2) group and oxaluric acid atom O(4). There is also a marginally close contact of 2·56 Å between adenine atom H(3) and parabanic acid atom O(4) which, considering the frequent participation of the C(8)–H group of purines in C–H···O hydrogen-bond-like interactions (Voet & Rich, 1970), may be taken as evidence for such an interaction.

Parabanic acid groups N(1)–H(1) and N(3)–H(2) form normal single hydrogen bonds to adenine atom N(3) and to oxaluric acid atom O(6), respectively.

The stacking relationships within the structure are illustrated in Fig. 3. It can be seen from this figure together with the close stacking contacts tabulated in Table 5 that the structure incorporates several types of stacking interactions in which there are a number of interatomic distances that are less than their minimal van der Waals contacts (Pauling, 1960).

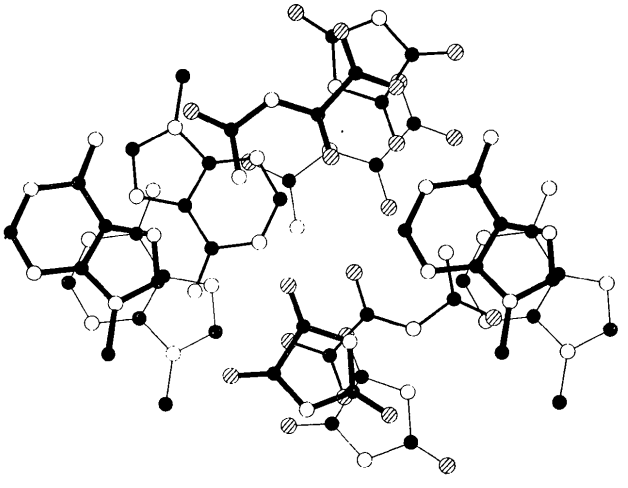


Fig. 3. A projection of three consecutive layers of the complex A.P.X.H_2O onto the plane of the parabanic acid rings. This illustrates the stacking relationships in the structure. Atoms are represented as circles of arbitrary radii with carbon atoms as filled circles, nitrogen atoms as unfilled circles and oxygen atoms as shaded circles. Hydrogen atoms have been omitted for the sake of clarity.

The parabanic acid molecules alternate in layers perpendicular to the *a* axis of the crystal with the carboxyl groups of the oxalurate ions. This can be seen in the upper right of Fig. 3. The close contacts within this grouping are clearly stabilized by Coulomb interactions among ionic charges and strong dipoles in a manner that has been discussed by Bolton (1964*a*). Oxalurate atom O(5) makes closer than van der Waals contacts with atoms C(4) and C(5) of the same parabanic acid molecule. Analysis of this system using the parameters suggested by Bürgi, Dunitz & Shefter (1974) indicates that the carbonyl groups are planar within experimental error (parabanic acid atom C(4) is 0·002 Å out of the N(3)–C(5)–O(4) plane in the direction of oxalurate atom O(5) and parabanic acid atom C(5) is 0·000 Å out of the N(1)–C(4)–O(5) plane) and that the oxalurate atom O(5) is rougly symmetrically disposed with respect to the molecular twofold axis of the parabanic acid molecule [XO(5*c*)–PC(4)–PO(4) = 98·0° and XO(5*c*)–PC(5)–PO(5) = 95·7°; XO(5*c*)–PC(4)–PC(5) = 71·6° and XO(5*c*)–PC(5)–PC(4) = 78·2°; XO(5*c*)–PC(4)–PN(3) = 97·5° and XO(5*c*)–PC(5)–PN(1) = 94·4°]. This system is distinguished from those studied by Bürgi, Dunitz & Shefter (1974) by the fact that a single oxygen atom [oxalurate atom O(5)] makes close contact with each of two covalently linked carbonyl groups.

The contact distance of 3·032 Å between adenine ethyl-group atom C(2′) and parabanic acid atom O(2*d*) is over 0·3 Å less than the corresponding minimal van der Waals distance of 3·4 Å (Pauling, 1960). However the shortest O···H contact distance between atom PO(2*d*) and the various adenine ethyl-group hydrogen atoms, the 2·65 Å contact with atom AH(10), is greater than the 2·6 Å minimum O···H van der Waals distance (Pauling, 1960). Therefore the close AC(2′)···PO(2*d*) contact can be attributed to crowding rather than to any sort of non-covalent bonding interaction.

The adenine residues form an alternating sandwich with the amide moieties of the same two oxalurate ions mentioned above. In this case the close intermolecular contacts appear to be stabilized by dipole–induced dipole interactions between the polar amide groups and the polarizable adenine ring system as has been discussed by Bugg (1972) and by Bugg, Thomas, Rao & Sundaralingam (1971). The adenine residue also is stacked on a centrosymmetrically related adenine residue in a manner quite similar to that found in the complexes 9-ethyladenine–5,5-diethylbarbituric acid (Voet, 1972) and 9-ethyladenine–5-isopropyl-5-bromoallylbarbituric acid (Voet & Rich, 1972) [see Fig. 8 in Bugg (1972)]. This interaction, which is illustrated somewhat obliquely on the left side of Fig. 3, is charac-

terized by normal contacts among the atoms of the two aromatic residues.

The water oxygen atom is within hydrogen bonding range of one donor group, oxaluric acid N(3)–H(3), and three acceptor groups, oxaluric acid atoms O(2) and O(6), and parabanic acid atom O(4). These interactions, which can be seen in Fig. 1, take place at the ends of a slit-like cavity in the unit cell that is occupied by two centrosymmetrically related water molecules. These water molecules, which are located 3·509 Å apart, appear to contact the walls of the cavity only in the area of these hydrogen-bonding regions. Hence the lack of forces holding the water molecule in place probably causes the water molecule to be somewhat disordered. This accounts for the difficulty in locating the water hydrogen atoms.

Discussion

The data presented in Table 3 permit the comparison of the corresponding bonding parameters of uncharged adenine residues and N(1)-protonated adeninium residues. These indicate that within the variations of the measurements there are no significant alterations of the adenine bond lengths upon N(1)-protonation. However such protonation causes a 4·9° average increase of the C(6)–N(1)–C(2) angle together with compensating 3·5° and 3·7° decreases, respectively, at the adjacent N(1)–C(2)–N(3) and C(5)–C(6)–N(1) ring angles. The latter decrease causes offsetting increases of 1·8° and 2·1°, respectively, at the neighboring N(1)–C(6)–N(6) and C(5)–C(6)–N(6) extra-annular angles involving the amine group. There are no other significant variations in corresponding bond angles between adenine and N(1)-protonated adenine residues. Therefore it appears that the main structural adjustment made by the adenine residue upon N(1)-protonation is a slight compression of its pyrimidine ring so that there is a relative movement of atom N(1) by 0·04–0·05 Å in the general direction of atom C(4).

Singh (1965) first pointed out that the internal angle at a nitrogen atom that is a member of a planar six-membered ring is about 10° larger for nitrogen atoms with an extra-annular attachment than for those without such a bond. Voet & Rich (1970) determined that in purines and pyrimidines the compensatory angular changes required to preserve the planarity of the hexagonal ring are largely localized at the positions adjacent to that at which the extra-annular attachment is made. The present study corroborates these observations but suggests that for N(1)-protonation of an adenine residue the magnitude of the angular adjustment is about half that deduced by Singh (1965) for six-membered heterocyclic rings.

Eight of the ten potential hydrogen-bonding acceptor sites of the adenine and the oxaluric acid molecules are definitely employed in the hydrogen-bonding network of the crystalline complex. The remaining two sites probably accept hydrogen bonds from the water molecule. In contrast, no more than one of the six potential hydrogen-bonding acceptor sites of the parabanic acid molecule participates in hydrogen bonding. This possible exception is the ostensible hydrogen bond from the water molecule to parabanic acid atom O(4).

The analysis of solid state N–H···O hydrogen-bonding parameters in which the acceptor goup is a carbonyl oxygen atom of a uracil derivative (Voet & Rich, 1970) or a barbiturate (Voet, 1975; Gartland & Craven, 1974) clearly indicates that such interactions with barbiturates are significantly longer (and presumably weaker) than with other molecules. Therefore it appears that electronic interactions among several carbonyl groups in close proximity can drastically reduce their abilities to act as hydrogen-bond acceptor groups. This hypothesis is corroborated by the fact that crystalline alloxan (5-oxobarbituric acid) forms none of the four intermolecular hydrogen bonds in which each molecule might be expected to participate (Bolton, 1964*b*). Gartland & Craven (1974) also showed that the N–H groups of barbiturates tended to form stronger than average N–H···O hydrogen bonds.

The present study was undertaken in order to ascertain the effect of eliminating atom C(5) of barbiturates (to form parabanic acid) on the hydrogen-bonding properties of their complexes both with adenine derivatives and in general. The lengths of the seven reported N–H···O hydrogen bonds in which the oxygen atom is a member of parabanic acid carbonyl group and the N–H group comes from some other type of molecule (Colman & Medlin, 1970*a*, *b*) range from 2·92 to 3·24 Å and average 3·11 Å. Hence the hydrogen-bond accepting properties of parabanic acid carbonyl groups resemble those of barbiturate carbonyl groups (Gartland & Craven, 1974). The failure of the carbonyl groups of the parabanic acid in the present study to participate in the hydrogen-bonding pattern of the structure further supports this hypothesis. The lengths of the four reported N–H···O hydrogen bonds in which parabanic acid supplies the N–H group and the oxygen atom comes from some other type of molecule (Colman & Medlin, 1970*a*, *b*) range from 2·67 Å (one of the shortest N–H···O bonds on record) to 2·95 Å. Therefore, the hydrogen-bonding properties of parabanic acid N–H groups cannot, at present, be readily correlated with those of barbiturate N–H groups.

In conclusion, then, the unusually large number of molecular components in the present structure associate in such a manner as to illustrate a wide variety of intermolecular interactions. However, the unexpected appearance of oxaluric acid presents serious difficulties in correlating these interactions with those of adenine–barbiturate complexes. Nevertheless the nature of the associations that parabanic acid both takes part in and appears to avoid, supports the hypothesis that the intermolecular association properties of parabanic acid are much the same as those of the barbiturates.

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